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γ-Methyl-substituted-γ-butyrolactones: solid-phase synthesis employing a cyclisation–cleavage strategy

Nicolas Gouault, Jean-François Cupif, Armelle Sauleau and Michèle David*

Laboratoire de Chimie Pharmaceutique, UPRES Pharmacochimie de Molécules de Synthèse et de Substances Naturelles, Faculté de Pharmacie, 2 avenue du Professeur Léon Bernard, 35043 Rennes, France

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Abstract

The solid-phase synthesis of several γ-methyl-substituted-γ-butyrolactones using a cyclisation–cleavage reaction is reported. Chemical modifications of polymer-bound azido (**2a**) and iodo alcohols (**2b**) were realised in order to introduce additional diversity onto the lactone structure.

Lactones are prominent moieties in biologically active compounds[1–4] and serve as versatile starting materials for other important compounds such as furans or cyclopentenones.[5]

Additionally, these subunits are attractive targets for solid-phase syntheses affording the opportunity to combine the cyclisation and resin cleavage steps in order to provide a traceless synthesis.

In previous studies[6] we attempted to prepare functionalised γ- and δ-lactones via resin-bound epoxides **1** (Merrifield resin) by ring-opening reaction with azides or thiophenates and subsequent cleavage. However, one limitation of our method was to introduce additional diversity by nucleophilic ring-opening reaction without affecting the ester linkage. In this paper, we describe the use of polymer bound azido (**2a**) and iodo alcohols (**2b**) as scaffolds for the synthesis of a large range of γ-methyl-substituted-γ-butyrolactones (Scheme 1). These scaffolds **2** were found to be useful intermediates for further transformations prior to detachment from the resin. Synthetic approaches starting from the polymer bound alcohols **2** with subsequent on-resin functionalisation and release by cyclisation are reported.

First, we investigated the conversion of azido-group **2a** into amides (Scheme 2) and triazoles (Scheme 3). The method for amide synthesis was carried out with resin-bound azides[6], acids and tributylphosphine (route (i)). Amines were unlikely intermediates in this protocol and the presence of an ester group in the linker meant that cyclisation to the lactam and internal resin cleavage

* Corresponding author. E-mail: michele.david@univ-rennes1.fr

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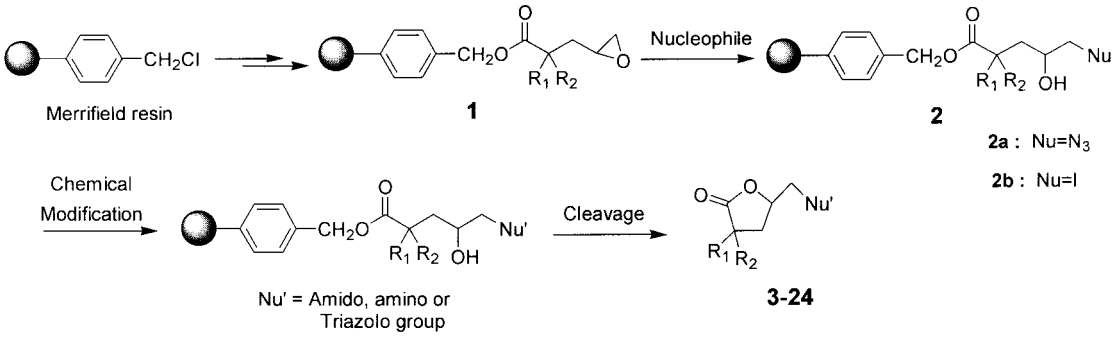
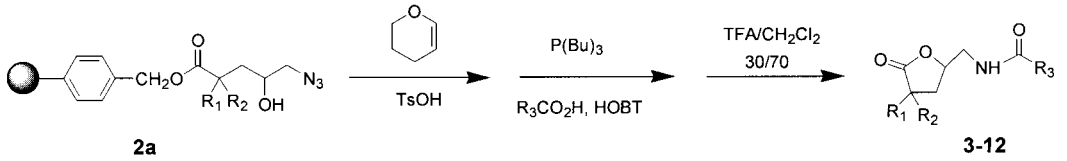
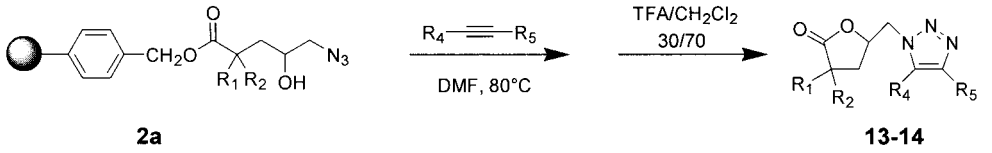


Scheme 1.

would occur leading us to use a one-pot reaction[7] to avoid this problem. The procedure involved the reaction between activated carboxylic acids in solution and resin-bound iminophosphorane generated (but not isolated) from the corresponding *O*-protected azido alcohol and tributylphosphine.



Scheme 2. Synthesis (route(i)) of lactones **3**–**12**

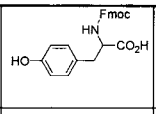
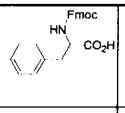
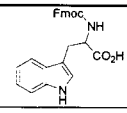
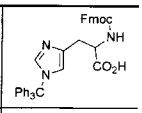


Scheme 3. Synthesis (route(ii)) of lactones **13**–**14**

After some experimentation, the best results were obtained when the acids or the *N*-Fmoc aminoacids were activated with diisopropylcarbodiimide (DIC) and hydroxybenzotriazole (HOBT) in THF (0°C). The solution was then treated with resin **2a** and tributylphosphine and stirred for 18 h. FTIR was successfully used to monitor the reaction since disappearance of absorption at 2100 cm^{-1} ensured complete conversion of the azide function. The observation of a band at 1680 cm^{-1} indicated the formation of an amide. Lactonisation was then initiated by trifluoroacetic acid (30% TFA/CH_2Cl_2, 4 h) to liberate after cleavage the γ-amidomethyl-γ-lactones (**3**–**12**)[8] in moderate yields (Table 1).

Another synthetic sequence (route (ii)) is presented which allows the solid-phase synthesis of substituted 1,2,3-triazoles (Scheme 3). While investigating the chemistry of the support-bound azido alcohol, we envisaged a 1,3-dipolar cycloaddition using acetylenic esters[9] in order to extend the variety of groups that can be incorporated into the butyrolactone structure.Thus, reaction of resin-bound **2a** with acetylenic esters in DMF (80°C, 12 h) gave lactones **13**–**14**[10] (Table 2).

Table 1

R_3CO_2H										
R_1,R_2	H,H	H,H	H,Me	H,H	H,Me	Me,Me	H,H	H,H	H,H	H,H
Lactone	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
% Yield[a]	48[b]	30	70[b,c]	70[b]	34[b,c]	20[b]	21[c,d]	20[c,d]	15[c,d]	13[c,d]

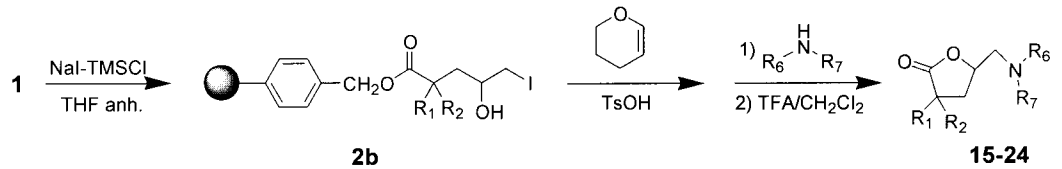
[a] Isolated yield after purification by chromatography. All the new products were identified by ^1H and ^{13}C NMR. [b]Crude yield. [c]1/1 mixture of diastereoisomers. [d]correlated ^1H-^{13}C NMR was necessary to assign all the signals.

Table 2

R_4—≡—R_5	R_1,R_2	Lactone	%Yield[a]	R_4—≡—R_5	R_1,R_2	Lactone	%Yield[a]
R_4=H R_5=CO_2Me	H,H	**13**	20	R_4= CO_2Me R_5=CO_2Me	H,H	**14**	35

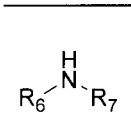
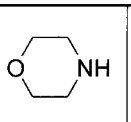
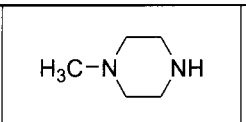
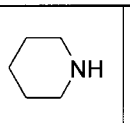
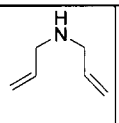
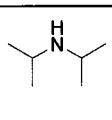
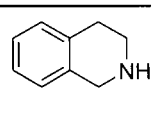
[a] Isolated yield after purification by chromatography. All the new products were identified by ^1H and ^{13}C NMR.

The second intermediate (iodoalcohol polymer-bound **2b**) was found to be convenient for introducing an amino group (Scheme 4). Ideally, we hoped to develop the direct aminolysis of epoxides **1**. However, classical conditions[11] which required a large excess of the amine in a protic solvent at elevated temperature or in a non-protic solvent through catalytic assistance of metal ion salts[12,13] were problematic on Merrifield resin due to the poor swelling and the cleavage of the ester linkage.We therefore chose a two-step synthesis of supported amino alcohols (route (iii)) involving ring-opening of the precursor **1** with TMSiI (generated in situ) then displacement of the iodide with secondary amines in DMF at 70°C for a variable time (ranging from 15 to 48 h). It is worth noting that the hydroxyl group must be protected (DHP) to avoid the oxirane formation. Cleavage was carried out as previously described and gave γ-aminomethyl-γ-butyrolactones **15**–**24**[14] in moderate yields. When the resin **2b** was directly treated with TFA, the iodomethyl lactone was isolated. Examination of the crude product by NMR showed the presence of this lactone in some cases, indicating that substitution had not been completely achieved (Table 3).



Scheme 4. Synthesis (route(iii)) of lactones **15**–**24**

Table 3

						
R_1,R_2	H,H	H,Me	H,H	H,Me	Me,Me	H,H	H,Me	H,H	H,H	H,H
Lactone	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
% Yield[a]	60[b]	25[c]	71[b]	30[c]	42	60[b]	30[c]	60[b,d]	25[b]	42

[a]Isolated yield after purification by chromatography. All the new products were identified by ^{1}H and ^{13}C NMR. [b]Crude yield.
[c]1/1 mixture of diastereoisomers. [d]major product: iodomethyl lactone.

In summary, we have developed solid-phase strategies for the synthesis of diverse γ-methyl-substituted γ-butyrolactones. Similar work on the construction of other heterocyclic systems using cyclative cleavage is in progress in our laboratory, as well as evaluation of their cytotoxic and antiviral in vitro activities[15].

Acknowledgements

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References

1. Dubs, P.; Stussi, R. *Helv. Chim. Acta*. **1978**, *61*, 990–997.
2. Mori, K. *Tetrahedron* **1989**, 3233–3298.
3. Caine, D.; Venkataramu, S. D.; Kois, A. *J. Org. Chem*. **1992**, *57*, 2960–2963.
4. Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Org. Chem*. **1998**, *63*, 2385–2388.
5. Grimm, E. L.; Reissig, H.-U. *J. Org. Chem*. **1985**, *50*, 242–244.
6. Le Hetet, C.; David, M.; Carreaux, F.; Carboni, B.; Sauleau, A. *Tetrahedron Lett*. **1997**, *38*, 5153–5156.
7. Tang, Z.; Pelletier, J. C. *Tetrahedron Lett*. **1998**, *39*, 4773–4776.
8. A typical procedure for the synthesis of lactone **4**: The polymer used for this synthesis was the Merrifield resin (1.7 mmol of Cl/g, 1% DVB). To a suspension of methylthioacetic acid (216 mg, 2.04 mmol) and HOBT (280 mg, 2.04 mmol) in dry THF (5 ml) at 0°C under a nitrogen atmosphere was added DIC (322 µl, 2.04 mmol). After stirring for 10 min the solution was treated with resin **2a** ($R_1 = R_2 = H$) OTHP protected (600 mg, 1.02 mmol) followed by a 97% tributylphosphine solution (382 µl, 1.53 mmol). The mixture was stirred for 18 h at room temperature under a nitrogen atmosphere, then filtered, washed and dried under vacuum. After cleavage with 30% TFA/CH_2Cl_2 (8 ml, 2 h), the solution was filtered from the resin, concentrated to dryness. Purification of the residue by chromatography on silica gel eluting with CH_2Cl_2:MeOH (95:5) gave pure lactone **4**: yield 30%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.20 ('s', 1H), 4.62–4.67 (m, syst.AMX, $J_{AM} = 14.6$ Hz, $J_{AX} = 7.3$ Hz, $J_{MX} = 7.0$ Hz, 1H), 3.77–3.82 (dd, syst.AMX, 1H), 3.34–3.40 (dd, syst.AMX, 1H), 3.22 (s, 2H), 2.55–2.62 (m, 1H), 2.30–2.40 (m, 1H), 2.13 (s, 3H), 1.90–2.00 (m, 1H). ^{13}C NMR ($CDCl_3$, 125MHz) δ 176.6, 169.2, 79.3, 43.3, 38.0, 28.5, 24.9, 16.4. EI-HRMS *m/z* 203.0645 ($C_8H_{13}NO_3S$ requires 203.0616).
9. Bastide, J.; Hamelin, J.; Texier, F.; Quang, Y. V. *Bull. Soc. Chim. Fr*. **1973**, 2555–2579.
10. A typical procedure for the synthesis of lactone **13**: To a suspension of the polymer bound alcohol **2a** ($R_1 = R_2 = H$) (600 mg, 1.02 mmol) in dry DMF (8 ml) was added methylpropiolate (0.9 ml, 10.2 mmol) under a

nitrogen atmosphere. The resulting mixture was heated at 80°C for 3 h. Procedure for cleavage was the same as described above. Compound **13** was obtained after purification by chromatography on silica gel eluting with CH_2Cl_2:MeOH (95:5); yield: 20%; white crystalline solid: m.p. 156°C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.30 (s, 1H), 4.87–4.93 (m, syst.AMX, $J_{AM} = 14.6$ Hz, $J_{AX} = 6.0$ Hz, $J_{MX} = 3.2$ Hz, 1H), 4.79–4.84 (dd, syst.AMX, 1H), 4.59–4.64 (dd, syst.AMX, 1H), 3.95 (s, 3H), 2.55–2.63 (m, 1H), 2.39–2.51 (m, 1H), 2.01–2.10 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.2, 160.8, 140.5, 128.8, 77.3, 53.4, 52.3, 28.0, 24.6. IR-FT: ν (cm^{-1}) 1716, 1770.

11. Mousseron, M.; Jullien, J.; Jolobine, Y. *Bull. Soc. Chim.* **1952**, 757–766.
12. Crotti, M. C. P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433–436.
13. Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericas, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309–6318.
14. A typical procedure for the synthesis of lactone **17**: *N*-methylpiperazine (1.13 ml, 10.2 mmol) was added to the OTHP-protected resin **2b** ($R_1 = R_2 = H$) (600 mg, 1.02 mmol) in dry DMF (10 ml) and heated at 70°C under a nitrogen atmosphere for 15 h. After cleavage, the residue was purified by chromatography on silica gel eluting with $CHCl_3$:MeOH (50:50); yield: 71% ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.70–4.75 (m, syst.AMX, $J_{AM} = 14.0$ Hz, $J_{AX} = 7.0$ Hz, $J_{MX} = 3.8$ Hz, 1H), 2.90–3.00 (m, 4H), 2.70–2.80 (m, 4H), 2.65–2.74 (m, syst.AMX, 2H), 2.62 (s, 3H), 2.50–2.59 (m, 2H), 2.29–2.37 (m, 1H), 1.90–2.00 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.8, 80.5, 62.5, 55.2, 52.8, 44.6, 29.2, 26.9. IR-FT: ν (cm^{-1}) 1768. EI-HRMS m/z 198.1372 ($C_{10}H_{18}N_2O_2$ requires 198.1368).
15. Gouault, N.; David, M.; Cupif, J. F.; Sauleau, A.; Amoros, M. *Pharm. Pharmacol. Commun.* **1999**, *5*, 159–163.